From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/001879	23.02.2005	01.03.2004

International Patent Classification (IPC) or both national classification and IPC
C07D217/18, C07D401/06, A61K31/472, A61K31/4725, A61P3/04, A61P25/00

Applicant
ACTELION PHARMACEUTICALS LTD

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	vanVoorsttotVoorst,M Telephone No. +49 89 2399-8280

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

AD SECTION V:

1. The following documents have been considered;

   D1: WO 01/68609 A (ACTELION PHARMACEUTICALS LTD; AISSAOUI, HAMED; CAPPI, MICHAEL; CLOZEL,) 20 September 2001 (2001-09-20)
   D2: WO 02/051838 A (ACTELION PHARMACEUTICALS LTD; AISSAOUI, HAMED; CLOZEL, MARTINE; WELLER) 4 July 2002 (2002-07-04)

2. The present compounds are considered to represent a novel selection from the derivatives of general formulae (I) and (II) disclosed in D1, wherein the novelty giving feature is seen in the presence of the trifluoromethyl-phenyl/pyridyl-ethyl group on position 1 of the 1,2,3,4-tetrahydroisoquinoline moiety.
   The compounds disclosed in D2 are not 1,2,3,4-tetrahydroisoquinoline compounds but are benzazepines or related heterocyclic derivatives.
   Having regard to the above the subject-matter claimed appears to comply with the requirements of Article 33(2) PCT.

3. Closest prior art comprises the 1,2,3,4-tetrahydroisoquinoline derivatives disclosed in D1, which possess similar pharmacological properties as the present compounds.
   The problem to be solved was to provide further 1,2,3,4-tetrahydroisoquinoline compounds, which are non-peptide antagonists of human orexin receptors.
   As indicated above, the compounds claimed represent a novel selection from the compounds of general formulae (I) and (II) disclosed in D1, accordingly, it is considered that the skilled person faced with the above problem would have expected this activity from the present compounds. Thus an inventive step could only be acknowledged, if the Applicant can show that the compounds claimed possess some unexpected effect or advantage over the known prior art compounds.
   As there is no indication found in the description, e.g. test data, which shows such an unexpected effect or advantage of the compounds claimed, an inventive step as required by Article 33(3) PCT cannot be acknowledged. The Applicant is requested to demonstrate, preferably by means of comparative tests, whereon an inventive step could be based.

4. No objections with regard to Article 33(4) PCT arise for claims 1-14.

AD SECTION VI:

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2004/085403	07.10.2004	23.03.2004	26.03.2003

The priority documents pertaining to the present application were not available at the time of establishing this written opinion. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the document cited above could become relevant to assess whether claims 1-14 satisfy the criteria set forth in Article 33(1) PCT.